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A PHYSIOLOGICALLY-BASED DESCRIPTION OF THE INHALATION PHARMACOKINETICS OF STYRENE IN RATS AND HUMANS

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INTRODUCTION

Physiologically-based pharmacokinetic (PB-PK) models describe the body in terms of discrete organs or discrete sets of organs lumped together based on common physiological characteristics. These tissue groups are defined with respect to their volumes and blood flows and to their partition coefficient for test chemical and the biochemical interactions (protein binding/enzymatic metabolism) of the test chemical in the various tissue groups. PB-PK models have potential for extrapolation from one dose level to another, from one route of administration to another, and from the test species to other mammalian species, including humans.

The pharmacokinetics of inhaled styrene were previously described in the rat (1). An attempt to describe these data with a classical compartmental model met with only limited success because of non-linear kinetic behavior at the higher inhaled concentrations (600 and 1200 ppm). In this study we have developed a PB-PK model to describe the kinetics of styrene in rats after either inhalation or after oral dosing. This model explicitly accounts for the non-linear behavior. Secondly, we show the ability to extrapolate from the PB-PK model for the rat to predict styrene inhalation kinetics in humans.

MATERIALS AND METHODS

In previous studies, groups of male rats were exposed to styrene for 6 hr at 80, 200, 600, and 1200 ppm (1). Blood and fat styrene concentrations were determined at various times during the 6 hr exposure and in the 18 hr period after the exposure. This set of eight time course curves encompassing blood and fat styrene at the four concentrations were the main data base for modeling. Blood data after oral dosing were from Withey (2). Blood and expired air styrene concentrations in human volunteers exposed to various concentrations of inhaled styrene were reported by Stewart et al. (3) and Ramsey et al. (4).

In our styrene model we used four lumped tissue groups - analogous to (I) highly perfused tissues (excluding liver), (II) muscle and skin, (III) fat and marrow, and (IV) organs with high capacity for styrene metabolism (essentially, liver). Biochemical constants in rats (V_{max} = 3.6 mg/hg and K_m = 0.36 mg/L) were determined by steady-state techniques. Other model parameters were collected from the literature. Volumes (as percent body weight), blood flows (as percent cardiac output), and tissue partition coefficients (relative to blood:air partition coefficients) are given in Table 1 for the rat. Cardiac output was 5.6 L/hr for a 0.30 kg rat and alveolar ventilation was 4.5 L/hr. Parameters for human (83 kg average body weight) were determined by scaling flows and V_{max} as the 0.7 power of body weight and organ volumes were assumed proportional to body weight. The blood:air partition coefficient for humans was set at 52 (5). In the lung part of the PB-PK styrene was assumed to be equilibrated between end alveolar air and oxygenated blood. A steady state solution was then used to calculate arterial styrene concentration. Simulations of the set of four mass-balance differential equations for this PB-PK model were done using a modified commercial software package - Advanced Continuous Simulation Language (Mitchell and Gauthier, Inc., Cambridge, MA). For further details see Ramsey and Andersen (6).

TABLE 1

PB-PK MODEL CONSTANTS FOR THE VARIOUS TISSUE GROUPS

Tissue Group	Volume (% Total)	Blood Flow (% Cardiac Output)	Partition Coefficient
I - (viscera, brain)	4	12	5.7
II - (muscle, skin)	73	42	1.0
III - (fat, marrow)	9	9	50
IV - (metabolizing tissues)	5	37	2.7
Blood (rat)	-	-	39

RESULTS AND DISCUSSION

Rats. For styrene inhalation by the rats, all eight blood and fat time curves at the four concentrations were well-represented by the same set of constants (Table 1) and the non-linearity in kinetic behavior was accurately modeled (Fig. 1). Predicted behavior was very sensitive to fat

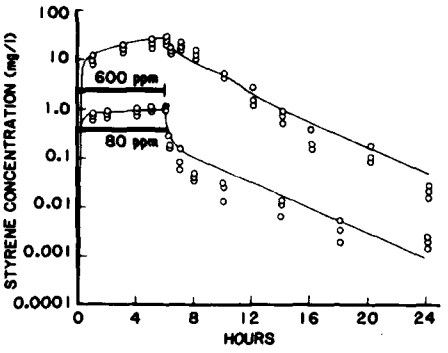

Fig. 1: Blood (styrene) in rats during and after 6 hr exposures to 80 or 600 ppm. Curves are from the model; data from Ramsey and Young (1).

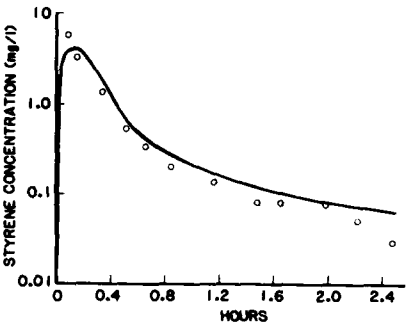

Fig. 2: Blood (styrene) in rats after an oral dose of 9.3 mg/kg. Data are from Withey (2); curves are based on PB-PK model with first-order input.

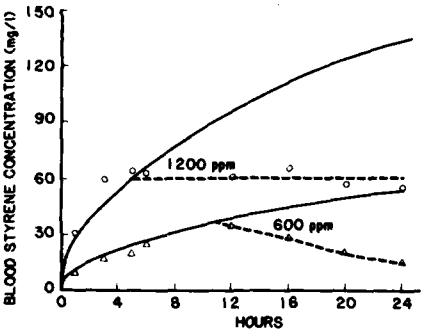

Fig. 3: Continuous 24 hr exposures in rats. Data from Ramsey and Young (1). Dotted curve accounts for enzyme induction (see text); solid curve does not.

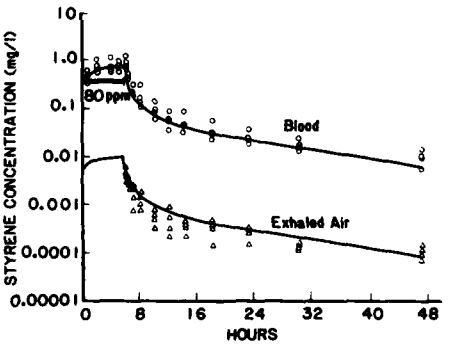

Fig. 4: Human exposure at 80 ppm for 6 hr. Data from Ramsey et al. (4), curves are from scale-up of the rat PB-PK model (see text).

compartment (III) parameters. The oral uptake of styrene dissolved in water was described with the same model except there was first-order input from stomach into the portal blood (Fig. 2). The best approximation to the data was with an input rate constant of 5.5 hr^{-1}. In 24 hr exposures to styrene, blood concentrations at later times were lower than predicted by the model (Fig. 3). This was apparently due to enzyme induction during the 24 hr period. A computerized optimization procedure was used with the PB-PK model to estimate the extent of induction and its time course. At 600 ppm there was a 3.4-fold increase in V_{max}, induction began after a lag-time of 10.6 hr and proceeded with a first-order rate constant of 0.32 hr^{-1}. At 1200 ppm, the increase was 4.4-fold, the lag-time was only 4.6 hr, and the rate constant was about 0.36 hr^{-1}. The ability to handle induction demonstrates the versatility of the PB-PK approach.

Human. The constants from the PB-PK model for rat were scaled to give a description of human kinetics and the predictions agreed closely with available data from the literature (Fig. 4). Other human data (3) were also well-described by this scaled-up model. The PB-PK analysis indicated that the non-linearities in kinetics would occur at the same inhaled concentration in humans as they did in rats (about 200 ppm). This study shows the extrapolative potential of PB-PK models for predicting human kinetics from a data base in other mammalian species. The ability to anticipate kinetic behavior in humans could very much improve human risk assessment procedures which are often based solely on a toxicity and pharmacokinetic data base from laboratory animals.

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